REMARKS

This amendment is responsive to the Office Action mailed January 12, 2005. Claims 30, 32, 33, 35-39, 41-65 are under examination.

Claims 43, 44, 47, 53, 55, and 56 have been amended herein to reference the full name of the gene (where applicable) or the name of the gene product which it encodes.

Specifically, Claim 43 has been amended to recite the β-aspartate semialdehyde dehydrogenase (*asd*) gene, support for which can be found on page 13, lines 27-30.

Claim 44 has been amended to recite the diaminopimelic acid (*dap*) gene, support for which can be found on page 13, lines 15-30; the alanine racemase (*dal*) gene, supported on page 15, lines 8-11; the D-alanyl D-alanine ligase (*ddl*) gene, supported on page 15, lines 19-25; and genes involved in fatty acid biosynthesis (*fab*), fatty acid degradation (*fad*), and phospholipid synthesis (*pls*), supported on page 16, lines 1-3.

Claim 47 has been amended to recite the gene encoding deoxyribonucleic acid polymerase I, (*polA*), support for which can be found on page 18, lines 1-6.

Claim 53 has been amended to recite the bacteriophage lambda promoter left or right (λP_L or λP_R) and to specify the temperature sensitive bacteriophage lambda *cI857* repressor, support for which can be found on page 6, lines 5-13.

Claim 55 has been amended to recite bacteriophage P22 components (promoters, *c2* gene), support for which can be found on page 8, lines 4-23.

Claim 56 has been amended to recite the bacteriophage lambda promoter left (λP_L), support for which can be found on page 6, lines 5-13.

Claims 35 and 65 have been amended to overcome the Examiner's objections under 37 C.F.R. §1.75(c). Claim 52 has been cancelled.

Additional amendments have been made to obviate remaining issues under 35 U.S.C. §112, second paragraph.

No new matter is presented.

Response to issues presented under 35 U.S.C. §112, second paragraph

Claims 43, 44-45, 47, 51, 53-55 and 60 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. Specifically, the Examiner objects to the use of abbreviations (when referring to particular genes) in the claims without first defining the abbreviation in the claims.

While Applicants agree with the Examiner that generally abbreviations should be defined in the claims, Applicants submit that in the case of genes, the abbreviation *is* the definition. It appears the Examiner's concern involves genes having the same or similar abbreviations, and therefore rendering the claims indefinite. However, the definiteness inquiry focuses on whether *those skilled in the art* would understand the scope of the claim *when the claim is read in light of the rest of the specification.* MPEP 2173.02; *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1576, 1 USPQ 2d 1081, 1088 (1986) (emphasis added). "[T]he definiteness of the language must be analyzed--not in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one possessing the ordinary level of skill in the pertinent art." *In re Moore, 439 F.2d 1235, 169 USPQ 236 (CCPA 1971).* The court in *In re Moore* further elucidated the above rule of law in a footnote, stating, "It is important here to understand that under this analysis claims which on first reading --in a vacuum, if you will--appear indefinite may *upon a reading of the specification disclosure* or prior art teachings become quite definite." *Moore,* 439 F.2d at 1235, 169 USPQ 238 (emphasis added).

Applicants submit that the genes which the Examiner alleges could be confused by those skilled in the art would be quite clear upon a reading of the specification. However, in an effort to advance the case to allowance, Claims 43, 44, 47, 53, 55, and 56 have been amended herein to reference the full name of the gene (where applicable), the name of the gene product that it encodes, or the source of the component (i.e., *bacteriophage* λP22 promoter right).

Applicants decline to amend the additional claims, for example, Claim 60 which refers to specific *Salmonella* genes and therefore cannot be confused with genes with similar names from other species. Such genes are commonly known in the art by their abbreviations appearing in the claims, and therefore Applicants submit the claims would be clear to any person of ordinary skill in the art. *In re Moore,* 439 F.2d at 1235, 169 USPQ 238.

Therefore, Claims 43, 44-45, 47, 51, 53-55 and 60 as amended, particularly when viewed in light of the specification, clearly apprise one skilled in the art of their meaning and scope and, thereby, serve the notice function required by 35 U.S.C. §112, second paragraph. Nothing more is required of Claims 43, 44-45, 47, 51, 53-55 and 60 under 35 U.S.C. §112, second paragraph.

In view of the foregoing amendments and remarks, reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph, are respectfully requested.

Response to issues presented under the judicially-created doctrine of obviousness-type double patenting

Applicants thank the Examiner for clearly setting forth her interpretation that serves as the basis of the imposed obviousness-type double patenting rejections, *viz.*:

> "**Please note:** The examiner is reading the phrase in independent claim 30 "under the control of an environmentally regulateable control sequence" to include within its scope a plasmid that comprises a control sequence for expression of the essential gene, wherein upon a change in the external physical environment of the bacterial cell, the plasmid would be lost resulting in the loss of the viability system and bacterial cell death. One such environment would be excretion of the bacterial cell outside the animal, an environment where DAP is not supplemented, thus defining an environment that lacks the selective pressure provided by DAP supplementation, resulting in bacterial cell death."

However, Applicants submit that this interpretation is not valid. What the Examiner refers to above is Applicants' previously disclosed technology known as "balanced-lethal" complementation (i.e., plasmid maintenance), which is described in Applicants' specification:

> "A preferred selection method involves a balanced-lethal host-vector system, where an essential gene is carried on a vector and the chromosomal gene is deleted, creating a balanced-lethal condition. The "lethal" deletion is balanced by the presence of the vector borne copy of the wild-type gene." (Page 12, lines 21-25 of the specification.)

The balanced-lethal technology was designed as an alternative plasmid maintenance technique to growing in the presence of antibiotics (with plasmid borne copy of an antibiotic resistance gene). A particularly preferred balanced-lethal involves a non-revertible mutation in the host's native chromosomal *asd* gene, which encodes the enzyme β-aspartate semialdehyde dehydrogenase. β-aspartate semialdehyde dehydrogenase is an essential enzyme for the synthesis of diaminopimelic acid (DAP), required for cell wall/membrane integrity. A copy of the native *asd* gene is then placed on a plasmid, e.g., an expression plasmid. Expression plasmids, depending on their size and/or energy demands, often carry with them selective pressure for not maintaining the plasmid, usually due to the high energy requirements originating from the plasmid. The balanced-lethal technology was developed to counter this selective pressure and to permit the survival only of the population of cells which retain the plasmid.

In creating an interpretation of the claims in which the present claims could be rejected under the doctrine of obvious-type double patenting in view of the "balanced-lethal" claims, the Examiner sets forth the following example/explanation:

> "a plasmid that comprises a control sequence for expression of the essential gene, wherein upon a change in the external physical environment of the bacterial cell, the plasmid would be lost resulting in the loss of the viability system and bacterial cell death. One such environment would be excretion of the bacterial cell outside the animal, an environment where DAP is not supplemented, thus defining an environment that lacks the selective pressure provided by DAP supplementation, resulting in bacterial cell death."

However, it is clear that the Examiner's interpretation and hypothetical situation are not tenable, as the hypothetical cell survives in all environments. The plasmid is not lost following excretion of the bacterial cell outside the animal. While the Examiner is correct that the outside environment is predominantly DAP-free, the plasmid is maintained due to the complementation system and DAP is produced internally. DAP in the Examiner's example does not provide the selective pressure, rather it is the absence of environmental DAP that serves to provide the selective pressure to maintain the plasmid, i.e., cells which fail to *maintain the plasmid* will die (independently of the presence or absence of environmental DAP). Applicants point out that the cells hypothesized by the Examiner survive in all environments (fermenter with or without supplemented DAP, in a host organism, e.g., a human where DAP is not provided, and in the outside environment). Applicants further point out that cells that randomly lose the plasmid and then die in an environment not supplementing DAP, whether it be in a fermenter, host, or some environment outside the host, are specifically excluded by the present claims which require the presence of the essential gene (*see* Claim 30, components (d)i – iv). Additionally, loss of the plasmid in that situation is a random occurrence rather than triggered by an environmental condition upon transfer from a permissive environment to a non-permissive environment.

In contrast to the Examiner's interpretation, the subject recitation "the Environmentally Limited Viability System comprises an essential gene that is under the control of an environmentally regulatable control sequence" refers to environmentally controlled, (e.g., activated or repressed) control sequences which serve as an "on/off" switch if you will, controlling the expression of particular genetic components in the ELV system, in this case, the essential gene. A particularly preferred essential gene is *asd*, which encodes the enzyme ß-aspartate semialdehyde dehydrogenase, which is an essential enzyme for the synthesis of diaminopimelic acid (DAP), required for cell wall/membrane integrity. This regulated, or

scheduled, expression of the essential gene and/or the lethal gene can be accomplished for example, by using various environmentally regulated promoter systems, e.g., the *ara*C-P_{BAD} system (induced in the presence of arabinose and repressed when arabinose is absent) or the temperature-regulated CI857 repressor system (active as a repressor at temperatures below 30°C).

U.S. Patent No. 6,780,405

In the Office Action, Claims 30, 32-33, 35-38, 50-60 were rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over Claims 1-24 of U.S. Patent No. 6,780,405 (hereinafter "the '405 patent"). Specifically, the Examiner contends that although the claims are not identical, they are not patentably distinct, stating:

> "the allowed species of method of inducing an immunoprotective immune response in a vertebrate anticipates the instantly claimed invention of inducing any type of immune response in an animal, wherein the composition administered in the instant Application comprises a bacteria that may or may not be attenuated, but the allowed species of microorganism must be attenuated, the viability system of the instant Application may be controlled by any number o[f] regulate[]able control sequences, but the allowed method administers a species which requires specific regulatory sequences."

Applicant traverses. The '405 patent claims are directed to regulated antigen delivery systems utilizing microorganisms containing a dual-*ori* (one low copy, one high copy) runaway vector (RAV) and at least one chromosome-encoded regulated repressor, in which the copy number of the RAV increases in response to reduced levels of the repressor responsible for repression of the high copy number *ori* of the vector. In operation, the RAD system allows for the foreign gene to be stably maintained on the plasmid at a low copy number, which is optimal during growing conditions (such as in a fermenter). Under desired conditions such as upon inoculation, however, the vector is activated into a "runaway" state by regulated de-repression of the high copy number *ori* and de-repression of foreign gene expression.

The object of the '405 patent is to design a system that produces and releases large amounts of antigen at a desired time, e.g., after inoculation. It is not seen how this RAV system can be considered an obvious variant of an ELV system designed for biological containment, i.e., to prevent the vaccine microorganism from surviving in selected non-permissive environments.

As the CAFC has stated regarding obvious-type double patenting:

> "Under that facet of the doctrine of double panting, we must direct our inquiry to whether the claimed invention in the application for the second

> patent would have been **obvious** from the subject matter of the claims in the first patent, in light of the prior art." *In re Longi,* 225 USPQ 645, 648 (Fed. Cir. 1985) (citing *Carman Industries Inc. v. Wahl,* 220 USPQ 481, 487 (Fed. Cir. 1983)). (Emphasis added.)

Merely because vaccination methods utilizing avirulent microbes expressing antigens exist in the prior art does not render Applicants' invention of improved vaccines containing biological containment systems obvious. The cited claims do not teach or suggest environmentally regulating the expression of the essential gene and/or actively lethal genes as a system to ensure biological containment of the vaccine microbe.

Therefore, since the methods of the present invention contain components and advantages not taught or suggested by the cited claims of record, Applicant requests reconsideration and withdrawal of the rejection under the judicially created doctrine of obvious-type double patenting.

U.S. Patent Nos. 5,294,441; 5,387,744; 5,855,879; and 5,855,880

Claims 30, 32-33, 36-38, and 41-43 were rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly being unpatentable over various claims of U.S. Patent Nos. 5,294,441; 5,387,744; 5,855,879; and 5,855,880.

Each of the cited patents involves claims to methods of generating an immune response to an antigen using particular attenuated pathogenic gram negative bacteria. Each patent contains an identical Claim 8, which incorporates the Applicants' previously patented "balanced-lethal" technology as a dependent claim, specifically:

> "wherein the cells of the strain:
> a) lack a functioning native chromosomal gene encoding beta-aspartate semialdehyde dehydrogenase (Asd);
> b) have present a recombinant gene encoding a functional Asd polypeptide which complements the chromosomal asd mutation, but which cannot replace the defective chromosomal gene by recombination;
> c) have a physical linkage between the recombinant genes encoding the functional Asd polypeptide and the immunogenic antigen, wherein the loss of the recombinant gene encoding the functional Asd polypeptides cause the cells to lyse when the cells are in an environment in which the lack of functional Asd causes the cells to lyse."

For the reasons set forth in the foregoing remarks, Applicants traverse. The cited claims refer to plasmid maintenance systems which ensure that the antigen-encoding vector is maintained in the vaccine

strain population. The present claims utilize an environment-triggered cell death to ensure that the vaccine strain cannot survive in particular environments (e.g., outside the host), as a biological containment system. It is clear that the "balanced-lethal" technology does not and cannot accomplish effective biological containment, because the vaccine cells survive in and out of the host due to the presence of the essential gene on the plasmid. What the balanced-lethal cells *do* ensure is that at any given time the surviving cell population will carry the desired plasmid (which the Examiner purports is lost when outside the vaccinee). While the present invention also contemplates the use of the balanced-lethal technology to maintain the plasmids, the balanced-lethal systems in no way render obvious a biological containment system that upon transfer to a pre-selected environment ceases expression of the essential gene and, in other embodiments, also begins expressing actively lethal genes. Accordingly, Applicants submit it is apparent that a system wherein some cells randomly (not regulatably) die in the designated non-permissive environment due to their failure to retain a plasmid when dividing, does not render obvious a system with an engineered environmental trigger that kills off the cell population upon transfer to the non-permissive environment.

Therefore, since the methods of the present invention contain components and advantages not taught or suggested by the cited claims of record, the present claims are NOT obvious variants of the prior patented claims and Applicants respectfully request reconsideration and withdrawal of the rejections under the judicially created doctrine of obvious-type double patenting.

In view of the amendments herein and the foregoing remarks, reconsideration and allowance of the claims as amended are respectfully requested.

Respectfully submitted,

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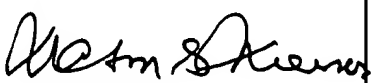
Signature: 

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